PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

02 JUN 2005

PCT

WRITTEN OPINION
(PCT Rule 66)

To:

DUBUC, J.
Goudreau Gage Dubuc
Stock Exchange Tower
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Montreal, Quebec H4Z 1E9
CANADA

Date of mailing *(day/month/year)*	25.10.2004
Applicant's or agent's file reference: ES/12987.27	**REPLY DUE** **within 3 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA 03/01893	03.12.2003	03.12.2002

International Patent Classification (IPC) or both national classification and IPC
C07D213/40

Applicant
BIOMEP INC.

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1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 03.04.2005

Name and mailing address of the international preliminary examining authority:

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I. Basis of the opinion

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

Description, Pages

1-121 as originally filed

Claims, Numbers

1-14 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 5-9 with regard to industrial applicability

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the Standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1,4
Inventive step (IS)	Claims	1-14
Industrial applicability (IA)	Claims	1-4,10-14

2. Citations and explanations

see separate sheet

Re Item I

Presently claimed subject-matter relates to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. Formula (I) is practically only made of variants (A, B, D, E, R, etc) which are defined by unspecific expressions like "zinc ligand", "zinc ligand bearing moiety", "substituted alkyl", "lower alkyl", "substituted lower alkyl", "lower alkoxy", "cycloalkyl", "aryl", "substituted aryl", "heteroaryl", "amino acid", "symmetrical disulfide", etc. The claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope was impossible.

Consequently, taking into account the compounds prepared in the examples and closely related homologous compounds, the International search report (ISR) has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds wherein A represents one of the groups listed and E is H, $CONHCH_3$, COOH, COOAlk, $CONH_2$, $CONHCH(COOH)CH_2OH$, CH_2CH_2OH, CH_2OH, CH_2COOH. The cases wherein R_1+ R_2, R_1+ R_3, R+ R_4, R_{11}+ R_1 and R_{11}+ R_2 may form a ring have not been searched.

Re Item III

Claims 5 to 9 are directed to methods for treatment of the human or animal body by surgery or therapy as well as diagnostic methods. They relate to subject-matter considered by this authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34 (4) (a)(i) PCT).

Under the terms of Rule 39.1(iv) PCT, the ISA was not required to carry out a search of such claims, but as indicated in the ISR, the search was carried out and based on the alleged effects of the compounds. Similarly, the IPEA (which is the ISA) is not required to carry out an International preliminary examination of such claims, but as for the ISR, the IPER will be based on the alleged effects of the compounds (Rule 67.1 (iv) PCT).

Re Item V

1. Cited documents

- D1: WO 03/084997
- D2: WO 99/11606
- D3: WO 97/05865
- D4: EP 0 412 595
- D5: FR 2 377 374
- D6: FR 2 372 804
- D7: CHEM. ABS., no. 43302, SERVAL, V. ET AL: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS (1992), 260(3), 1093-100
- D8: CHEM. ABS., no. 271122, CHAPMAN, KEVIN T. ET AL: JOURNAL OF MEDICINAL CHEMISTRY (1993), 36(26), 4293-301
- D9: CHEM. ABS., no. 41995, HAMAD ELGAZWY, ABDEL-SATTAR S.: MOLECULES [ELECTRONIC PUBLICATION] (2000), 5(4), 665-673
- D10: CHEM. ABS., no. 1980, OVENS, ANNABEL ET AL: JOURNAL OF PEPTIDE SCIENCE (2000), 6(9), 489-495
- D11: CHEM. ABS., no. 201580, RINNOVA, MARKETA ET AL: TETRAHEDRON LETTERS (2002), 43(22), 4103-4106
- D12: EP 0 254 032
- D13: EP 0 566 157
- D14: ROWE P S N: CURRENT OPINION IN NEPHROLOGY AND HYPERTENSION, vol. 7, no. 4, 1998, pages 367-376
- D15: BOILEAU GUY ET AL: BIOCHEMICAL JOURNAL, vol. 355, no. 3, 1 May 2001 pages 707-713
- D16: MIMURA, TETSUTARO ET AL: JOURNAL OF MEDICINAL CHEMISTRY (1992), 35(3), 602-8
- D17: WO 00/50580
- D18: FOURNIE-ZALUSKI, MARIE CLAUDE ET AL: LIFE SCIENCES (1982), 31(26), 2947-54
- D19: WO 02/15918
- D20: WO 02/092128

2. Novelty

In spite of the limitations done at the level of the ISR, numerous compounds have been found which fall in the presently claimed scope (see compounds disclosed n D1 to D11).

The novelty of the invention must be clearly established. The essential structural criterion, which is necessarily common to all the claimed compounds in order to fulfill the requirement of unity of the invention, must be unequivocally apparent. Such a feature must be also clearly essential to the claimed activity (see following inventive step).

3. Inventive step

3.1 According to the description, the problem underlying the present application is to provide selective PHEX inhibitors (pages 5-6) which can be used as osteogenic agents.

The Applicant says on page 5, lines 26-28, that with the present invention it was discovered that when the N-terminal amino acid or analog thereof is characterised by a side chain bearing an ionizable acidic group at physiological pH, an entirely new class of zinc metallopeptidase inhibitors, more specifically selective of PHEX, can be delineated.

D15 teaches that "PHEX appears unique (...) in that its S_1' pocket can accommodate negatively charged amino acid chain" and that "osteocalcin, pyrophosphate and P_i function as PHEX inhibitors (...): these molecules have negatively charged groups that may interact with the S_1' pocket of the enzyme". D16 allows, thanks to table II, to figure out what can be understood as a group accommodating the S_1' pocket. This teaching (confirmed in D19) appears to show that there is no real "discovery" in the invention as stated by the Applicant on page 5.

Additionally, some of the known compounds which destroy the novelty are also proteinase inhibitors and more specifically the compound in D8 is disclosed as a MMP inhibitor. In the light of the Applicant's comments which explain the similarities of the PHEX protein and other metallopeptidases, the skilled person would expect that this compound has also the claimed property.

Similarly the homologies demonstrated (pages 1-2, bridging paragraph) between PHEX protein and neutral endopeptidases (NMEP) which are zinc-containing glycoproteins lead the skilled person to expect similar properties. In this sense, the present invention can appear partly as a selection from D12 and D13, taking into account the overlapping scopes.

Once the novelty established, especially by specifying at least one characteristic common to all the claimed compounds, it must be shown that an unexpected effect is connected with this characterising feature of the invention and, consequently, that the acknowledgement of an inventive step can be based on it.

3.2 The Applicant's attention is drawn to the fact that the claims as presently drafted do not fully satisfy PCT requirements. Particularly, the protection which is sought should comply with a reasonable breadth of a scope covering only variants/compounds which solve the problem underlying the invention.

It is realized that the Applicant is entitled to claim all obvious modifications of what was concretely described, *i.e.* a certain number of examples, and that alternative variations have to be supported by the description.

Open (generalizing) expressions/terms like *zinc ligand*, *zinc ligand bearing moiety*, *substituted alkyl*, *lower alkyl*, *substituted lower alkyl*, *lower alkoxy*, *cycloalkyl*, *aryl*, *substituted aryl*, *heteroaryl*, *amino acid*, *symmetrical disulfide*, etc, derivatives thereof used throughout the claims including an irrealistic amount of variant possibilities extend the scope of the claims far beyond what has actually been investigated by the inventor(s). They render the claims **obscure in scope** and do not allow to correctly define a scope for which protection could actually be granted.

In view of the examples, unlimited definitions appear ***speculative***. Presently all prepared compounds correspond to well-defined structures wherein the substitution pattern is limited and represents a relatively narrow illustration of the claimed scope (see limitations of the search: the compounds wherein A represents one of the groups listed and E is H, $CONHCH_3$, COOH, COOAlk, $CONH_2$, $CONHCH(COOH)CH_2OH$, CH_2CH_2OH, CH_2OH, CH_2COOH. and the cases wherein R_1+ R_2, R_1+ R_3, R+ R_4, R_{11}+ R_1 and R_{11}+ R_2 may form a ring have not been searched). It can be questioned whether recurrent features are also necessary characteristics which should not be allowed to vary out of a ***reasonable*** extent of the usual equivalents and (bio)isosters of these variants.

The extent of a "reasonable generalisation" also depends on the extent of the illustration and also upon the relative distance to the prior art compounds

There is indeed a great variety of structural possibilities which are claimed and not yet explored by the Applicant, the *effect of which cannot be foreseen* having regard to the problem underlying the present application and consequently which are not solutions of the problem. The meanings of the substituents are also to be considered in view of the reproducibility and the feasablity of the invention in all its claimed aspects. Thus it is not clear whether the compounds implied fall within the scope of the claims of the present application and/or constitute a solution to the problem underlying the application.

As chemical species can be precisely defined for the disputed expressions or terms, it is necessary to specify them by means of the definitions given in the specification. It is additionally noted that the expression "but not limited to" used in certain definitions is an unspecific term. It cannot serve as a support for the invention and therefore should be deleted. It is also noted that definitions are given in the specification which do not correspond to any term (*e.g.* analogs, prodrugs, etc) of the claims and therefore are superfluous since they do not provide any supportive purpose.

In conclusion, the inventive step required by Article 33 (3) PCT can be acknowledged only for a well-defined scope embracing a reasonable generalisation of the very invention as illustrated. In other words, the protection which is sought should comply with a reasonably broad claimed scope such that it comprises only variants which are able to solve the problem underlying the invention, *i.e.* a prerequisite for the acknowledgement of an inventive step.

3.3 Any newly filed claims have to satisfy the criteria set forth in Article 33 (1) PCT. The Applicant will have to bring the description into conformity with these claims; care should be taken during revision, especially of the introductory portion including any statement of problem or advantage, not to add subject-matter which extends beyond the content of the application as originally filed (Article 34 (2)(b) PCT).

4. Miscellaneous - Inconsistencies

Compounds 114, 138 and 144 do not belong to the claimed domain of claim 1. Note that not ALL the said "examples" do actually illustrate the compounds of the invention:

for reason of consistency and clarity, it should be more appropriate to distinguish reference examples, intermediate examples, final compound examples, assay illustrations, etc.

Expressions "the alpha-substituent (P1 substituent)" (page 72) and "the P'2 substituent" (page 75) are not straightforwardly comprehensible from the description.

The expression "incorporated by reference" is misleading and unnecessary if the invention is properly defined as it should regularly be.